

# Exhibit A

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## "HOT-DOG" HEADACHE: INDIVIDUAL SUSCEPTIBILITY TO NITRITE\*

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**Summary** A patient who had noted the development of headaches shortly after eating frankfurters agreed to a series of tests aimed at determining whether the nitrites in frankfurters were the cause of his "hot-dog" headaches. He drank odourless and tasteless solutions containing 10 mg. or less of sodium nitrite or solutions identical in appearance containing 10 mg. of sodium bicarbonate. Headaches were provoked eight out of thirteen times after the ingestion of sodium nitrite, but never after the control solution. Headaches were also provoked by the ingestion of solutions containing 100 mg. of tyramine hydrochloride. The mechanism of headache production by these exogenous chemicals is uncertain.

### Introduction

Foods capable of inducing headaches in certain patients include chocolate, cheese, citrus fruits, and alcohol as the commonest offenders.<sup>1</sup> Although "dietary migraine" has been ascribed to an allergy to food, there has been no compelling evidence to support this hypothesis. Tyramine, a vasopressor agent and a constituent of some of these foods, has been shown to induce headache when given to susceptible patients.<sup>1,2</sup> Monosodium glutamate has been shown to cause "Chinese-restaurant syndrome", in which headache may be a prominent feature.<sup>3</sup> We have seen several patients in whom varying degrees of headache were experienced shortly after the ingestion of frankfurters or other cured-meat products. Evidence implicates the nitrite content of these foodstuffs as the cause of the "hot-dog" headache.

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Cured meat often contains sodium nitrite. Observations that metallic-nitrate impurities in rock salt were related to the red patches in cured meat led to the deliberate use of fixed concentrations of salt and nitrate to produce a more uniformly coloured product. Further investigations showed that the active colouring agent was not sodium nitrate but sodium nitrite, which is formed in meat by the bacterial and chemical reduction of nitrate; nitrites have thus been substituted for nitrates in the curing process. Nitrite and its decomposition product, nitric oxide, react with myoglobin and haemoglobin to form red compounds—nitrosomyoglobin and nitrosohaemoglobin.<sup>4</sup>

Although governmental regulations limit the nitrite levels reached during the treatment of cured meats to 200 p.p.m. (200 µg. per g. of meat), cooking and storage lead to a reduction in the nitrite content of meat so that the range of nitrite concentrations in cured meat is approximately 50 to 130 p.p.m.<sup>5</sup>

### Case-report

For 7 years a 58-year-old man noted bitemporal, moderately severe, nonthrobbing headaches within 30 minutes of eating normal quantities of cured-meat products such as frankfurters, bacon, salami, and ham. These attacks commonly lasted several hours, sometimes accompanied by facial flushing. By exclusion of cured meats from his diet, he has not had similar headaches, except those which occurred after inadvertent consumption of a cured-meat product. No other foods or beverages produced headache and he did not otherwise experience headaches. Recurring headache has not been noted in any members of his family.

### Methods and Results

10 mg. sodium nitrite or 10 mg. of sodium bicarbonate in aqueous solution were randomly administered

ADMINISTRATION OF SOLUTIONS CONTAINING SODIUM NITRITE TO A PATIENT WITH A HISTORY OF "HOT-DOG" HEADACHES

Amount ingested (mg.)	Time of onset of headache after ingestion (min.)	Duration of attack (min.)	Flushing	Headache
0.5	30	60	+	+
0.5	20	80	+	+
0.5	..	..	-	-
1	40	90	-	+
1	..	..	-	-
5	45	30	-	+
5	50	90	+	+
5	..	..	-	-
10	30	60	-	+
10	..	..	-	-
10	30	120	+	+
10	45	90	-	+
10	..	..	-	-
Total	35	80	4/13	8/13

approximately every other day over 2 months; the doses of nitrite administered approximated to the nitrite content of a small portion of cured-meat product. The nitrite and bicarbonate solutions were identical in both taste and appearance. The patient was told that the solutions might contain extracts of food substances which could produce a headache.

The subject was tested eight times with sodium bicarbonate solutions. He reported no headaches on

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those days. However, eight headache episodes were provoked during thirteen trials with nitrite solutions (see accompanying table). Flushing accompanied four of the eight headache attacks. The headaches were typical of his usual attacks, in that they were bitemporal and were dull and aching; there were no associated visual symptoms and he did not become nauseated. The headaches began about 35 minutes after the ingestion of sodium nitrite and lasted approximately 80 minutes. More severe headaches resulted from larger nitrite doses. Tyramine hydrochloride, in 100 mg. doses, also produced headaches in this subject within 45 minutes after ingestion in two out of four trials and were identical in character to the nitrite-induced episodes.

In ten volunteers with no history of food-induced headaches, neither sodium bicarbonate, nor sodium nitrite, nor tyramine hydrochloride provoked headaches.

## Discussion

Sodium nitrite may now be added to the other food factors, tyramine and monosodium glutamate, which can provoke headache in man. The mechanism underlying this ability is not clear. Tyramine was initially implicated in a syndrome of intense throbbing headache, and often hypertension, which resulted when some patients receiving antidepressant monoamine-oxidase inhibitors ate certain foods, some of which were subsequently shown to be rich in tyramine.<sup>6</sup> Potentiation of the pressor effects of tyramine by inhibition of its degradation seems to be an important mechanism in the pathogenesis of this syndrome.<sup>7</sup> However, it is unlikely that an increase in circulating tyramine is the only factor involved in these disorders, since chocolate, the food most commonly implicated in dietary migraine and the precipitant of at least one monoamine-oxidase inhibitor reaction,<sup>8</sup> contains very little tyramine.<sup>1</sup> The basis of the "Chinese-restaurant syndrome" has yet to be determined. It has been suggested that glutamate releases acetylcholine at neuromuscular junctions<sup>9</sup> and/or inhibits the transport of glucose into the brain.<sup>10</sup> In our patient a headache developed after the ingestion of tyramine as well as after sodium nitrite, which raises the possibility of a common humoral mediator or locus of action for these two chemicals.

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## BENIGN SICKLE-CELL ANAEMIA

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**Summary** Clinical, haematological, genetic, chemical, and oxygen-affinity studies have been carried out on a group of 18 Shiite Saudi Arabians with sickle-cell anaemia. Apart from occasional attacks of mild musculo-skeletal pain they are well and have few of the complications which are usual in the sickling disorders. The unusually mild course of the illness is attributable, at least in part, to a genetically determined ability to produce large amounts of fetal haemoglobin.

## Introduction

ALTHOUGH it was thought originally that the homozygous state for the sickle-cell (Hb S) gene was incompatible with survival to adult life, it is now apparent that this is not so.<sup>1,2</sup> However, most adult patients with sickle-cell anaemia are incapacitated to a variable degree by the disorder, and their lifespan is probably shortened considerably.<sup>1</sup> We report here the results of clinical and chemical studies on a group of individuals homozygous for sickle-cell anaemia, in many of whom the disease is almost completely symptomless. This appears to result from the presence of relatively large amounts of fetal haemoglobin in their red blood-cells.

## Material and Methods

The subjects were all Shiite Saudi Arabians of the Qatif or Al Hasa Oases. They were employees, or their dependants, of the Arabian American Oil Company (ARAMCO). The 18 persons with sickle-cell anaemia described in this study represent only a small proportion of the total number with this condition encountered in the ARAMCO hospital or clinics since 1958. They were selected randomly for detailed study so as to include adult males and females and adolescent subjects with relatives available for study. They had been followed for an average period of 11 years in the outpatient clinics. In most cases the condition was diagnosed on routine haemoglobin electrophoresis as part of a survey being undertaken currently by one of us (R. P. P.), or on routine clinical examination. Each patient had a complete physical examination together with a chest, straight abdomen, and gallbladder X-ray, and a 12-lead electrocardiograph (E.C.G.). A skeletal survey was undertaken which included X-rays of the spine (all cases), upper and lower extremities (14 cases), pelvis (11 cases), and skull (9 cases). The cardiac size was assessed clinically and radiologically. For comparison of height and weight, 200 male and 52 female Shiite Saudi Arabians attending the medical centre were examined.

In addition, blood-samples from 12 Jamaican patients with sickle-cell anaemia were collected and flown to Liverpool, in order that the structure of the associated Hb F could be compared with that of the Arabian patients.

*Hematological techniques* followed standard methods.<sup>3</sup> Blood-samples for haemoglobin analysis were collected into acid/citrate/dextrose solution or heparin and transported to Liverpool or London by air at 4°C.

*Haemoglobin analysis.*—The intracellular distribution of